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EFFECTS OF HIGH OXYGEN PRESSURE ON CARBON DIOXIDE TRANSPORT, ON BLOOD AND TISSUE ACIDITY, AND ON OXYGEN CONSUMPTION AND PULMONARY VENTILATION^{1,2}.

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UNTIL recent years there was a common belief that control of respiration was due to some relatively simple regulatory mechanism, for instance, the hydrogen ion concentration of the arterial blood. In the light of later experiments and more detailed correlation of existing data [Gesell, 1929] it would seem that control lies not in any one, but, rather, in a complex of closely inter-related factors bearing on the acidity and oxidative state of the respiratory centre.

One of these factors is the coordination of the dual function of the hæmoglobin [Gesell, 1923]. From the work of Christiansen, Douglas and Haldane [1914] it would seem that any condition which leads to a failure in reduction of hæmoglobin and the consequent lack of liberation of base at the tissues must interfere with the normal removal of carbon dioxide from the body and lead to an alteration in respiratory activity. It has been suggested that among other conditions causing such failure in reduction of hæmoglobin is exposure to oxygen at increased barometric pressures [Gesell, 1923]. This author [1923] states: "In view of the possible disturbance of the transport of acid, the problem of oxygen poisoning needs reanalysis."

It was for the purpose of determining more fully the significance of this disturbance in acid transport as a factor in respiratory control and as a contributing factor in oxygen poisoning that the present study was undertaken.

¹ Preliminary report: *Proc. Soc. Exp. Biol. and Med.* 1929, 26, 832.

² A dissertation submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

METHODS.

A suitable pressure chamber, supplied with accessory equipment for continuous registration of ventilation, oxygen absorption, blood acidity changes, volume flow of blood, blood-pressure, and pulse rate was constructed (Figs. 1, 1 A, 2, 3).

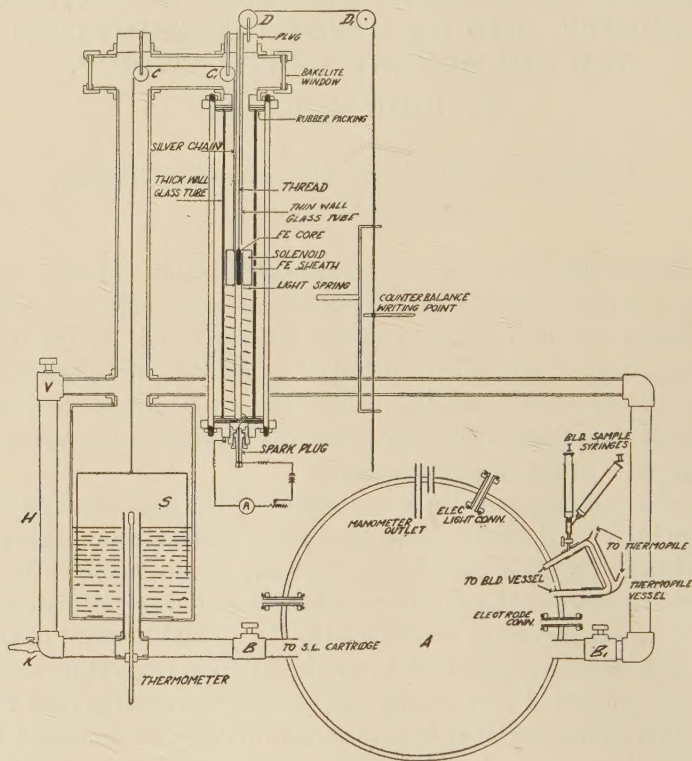


Fig. 1. Pressure chamber, spirometer and device for recording respiration. Thermopile vessel and connections as well as blood sample syringes are shown.

The recording of pulmonary ventilation and oxygen consumption was accomplished by means of a spirometer (*S*, Fig. 1) of the Hutchinson type. Provision was made within the chamber for a soda-lime cartridge with inspiratory and expiratory valves. The bell and water seal were entirely enclosed within a steel cylinder and subjected to the pressure obtaining in the chamber *A* by means of the pipe connections *B* and *B*₁. The counterbalance for the bell was a solenoid exposed to chamber pressure. The magnetic field set up by passage of a current through the

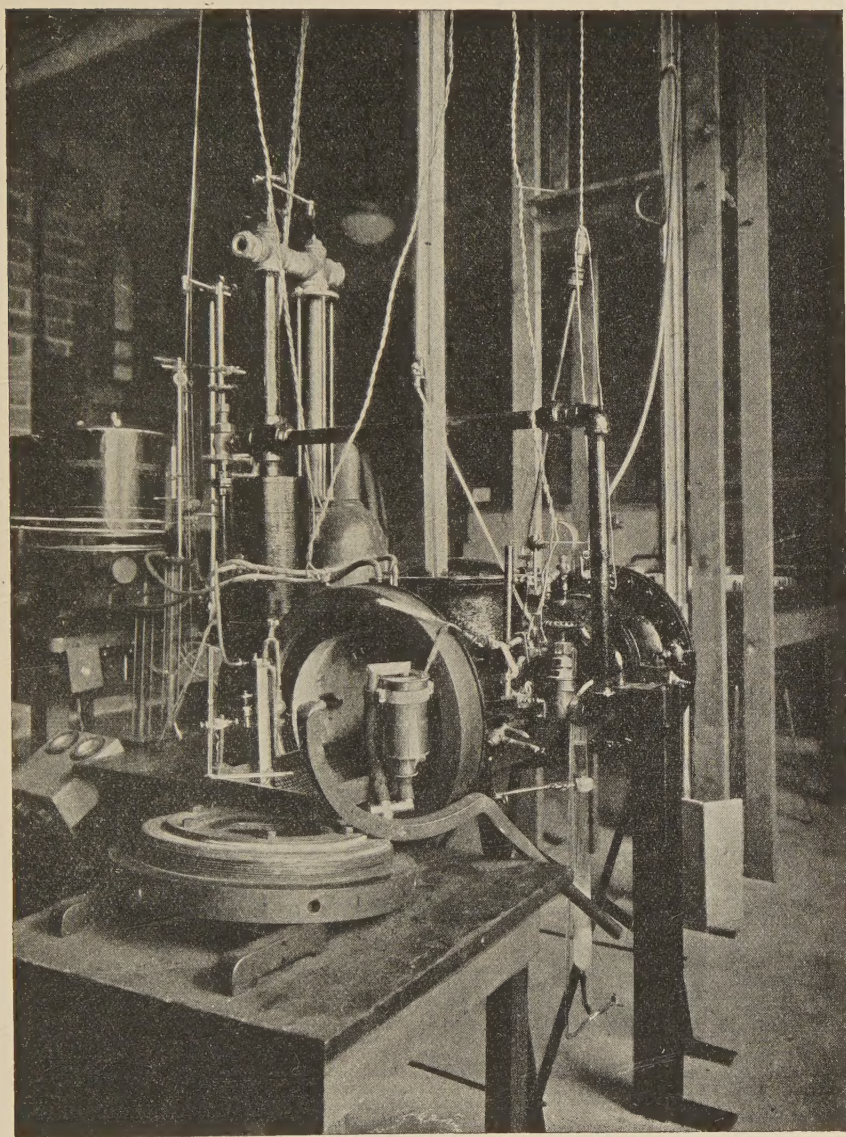


Fig. 1 A.

solenoid and acting on the counterbalanced iron core located outside the chamber, served to record pulmonary ventilation and oxygen consumption (see Fig. 1). From the same figure it is seen that the solenoid circuit is made up of battery, central binding post of an automobile spark plug, a very light and flexible wire coil spring, solenoid, silver chain (amalgamated), brass pulleys CC_1 , ground, ammeter, and rheostat. The iron core and its writing-point counterbalance are suspended by silk thread thrown over pulleys D and D_1 . Test records made with this apparatus are shown in Fig. 4 B.

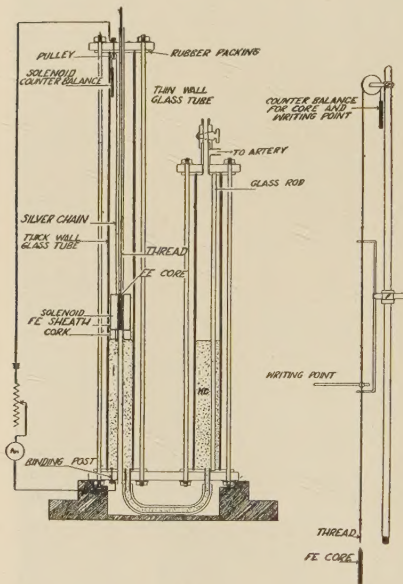


Fig. 2. Blood-pressure manometer, and method of recording blood-pressure.

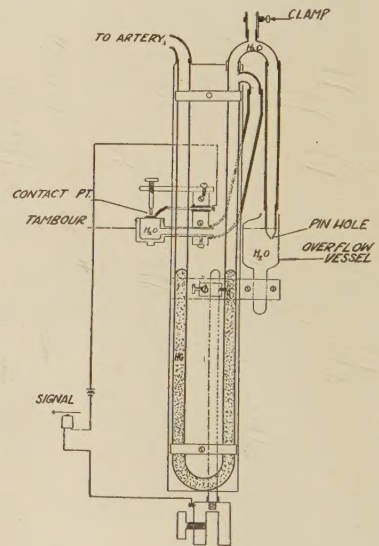


Fig. 3. Apparatus for recording pulse rate electrically.

In the construction of a manometer (Fig. 2) to give a record of blood-pressure on smoked paper, essentially the same principle as used in recording ventilation was employed, but in this case the solenoid floated on the mercury. One arm of the manometer was connected through the chamber wall to the artery and the other by pressure tubing to the chamber for pressure equalization. The diagram shows this solenoid circuit to be made up of battery, variable resistance, ammeter, binding post, mercury, solenoid, silver chain (one end of solenoid winding dipped into the mercury and the other soldered to the silver chain), pulley and its binding post. Test records obtained by this new apparatus and those

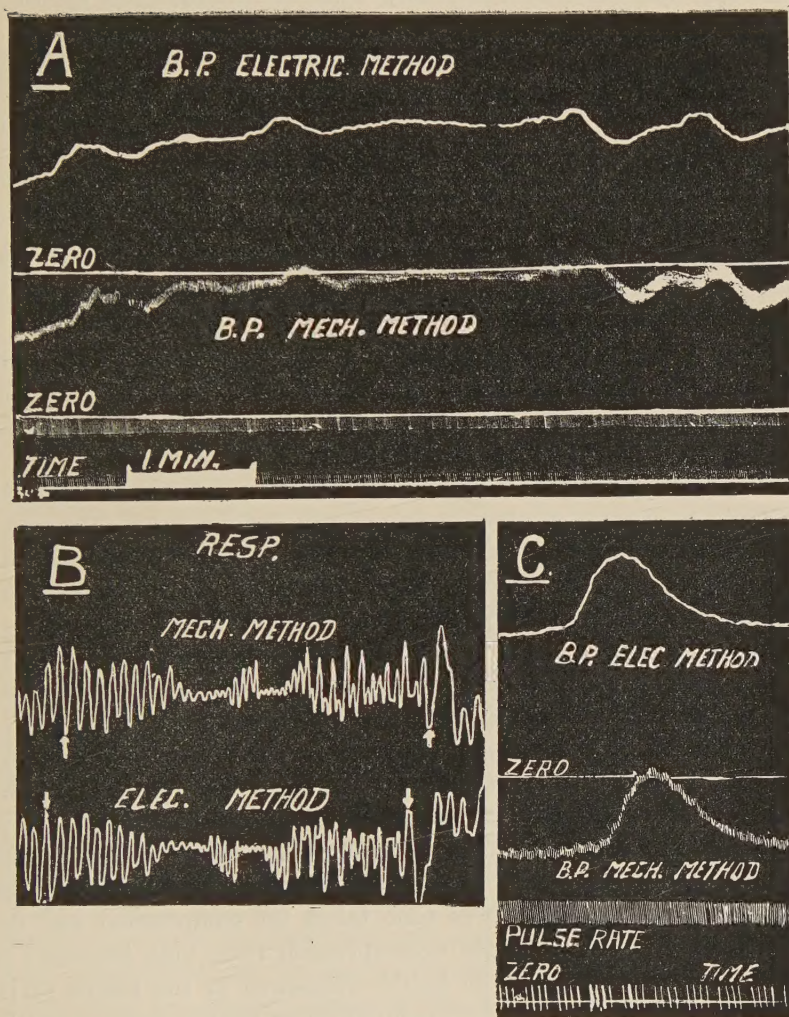


Fig. 4. A. Simultaneous tracings of blood-pressure obtained by mechanical method and by electrical method. B. Tracings obtained simultaneously by mechanical and by newly designed electrical method for recording respiration. C. Simultaneous tracings of blood-pressure and pulse rate as obtained by usual mechanical method and by the electrical method.

obtained simultaneously in the usual manner are shown in Fig. 4 A, C. Heart rate was recorded electrically with the arrangement shown in Fig. 3.

Acidity changes were followed graphically by the use of the manganese-dioxide electrode [Gesell and Hertzman, 1926], the potentiometer connections being led out of the chamber *via* electrode connections (see Fig. 1). Acidity changes were also determined in one series of experiments by obtaining samples of fresh circulating blood by means of syringes I and II (Figs. 1 and 1 A). In experiments on volume flow of blood the thermo-electric method of Gesell and Bronk [1926] was used. The blood was led through insulating tubes to the thermopile vessel (Fig. 1) located outside the pressure chamber.

All experiments were done on dogs (5 to 12 kg.) anaesthetized with morphine sulphate and urethane. In all those experiments on volume flow of blood, and those in which the electrode was placed in the circulating blood, heparin was injected intravenously as anti-coagulant.

The oxygen pressures used ranged between four and five atmospheres developed in periods of about four minutes from commercial oxygen tanks. More rapid compression, it was found, resulted in too marked a rise of temperature within the compression chamber. Exposures were regulated to avoid so far as possible the development of the convulsive state as observed by Bert [1878], Hill and Greenwood [1907 *a*], Smith [1899], Hill and Macleod [1903 *a, c*]. Another consideration taken into account in regulating the length of exposure was the apparent effect of oxygen in decreasing the anaesthesia. This has been noted by Davidson [1925] with other anaesthetics. In a few cases, therefore, the attempt to produce anaesthesia for the desired time resulted in excessively deep anaesthesia. The duration of exposure to oxygen varied somewhat, but in the greater number of experiments it was from fifteen to thirty minutes, exclusive of time taken for compression and decompression. While very rapid decompression from high pressures of oxygen may possibly result in bubble formation in the tissues [Hill and Greenwood, 1907 *a*], there is no evidence that it occurred in the present experiments. Nevertheless, the decompressions were carried out slowly except in those cases where lowered anaesthesia required rapid decompression. In all but a few instances in which the pressure was decreased very gradually and continuously, decompression was carried out by half stages. The intervals between stages, however, were not progressively lengthened as set forth by Boycott, Damant and Haldane [1908] in their report on the decompression of divers.

RESULTS.

A preliminary series of seven experiments was run with the purpose of determining the acidity change, if any, which occurred in the circulating arterial blood of animals exposed to about three atmospheres of pure oxygen. The manganese-dioxide electrode was used and placed with the calomel cell inside the compression chamber. In these preliminary experiments which were run before a method of recording respiration had been developed, no spirometer was used. The animals breathed the chamber oxygen through a soda-lime cartridge provided with inspiratory and expiratory valves. The soda-lime was renewed before each experiment. The records obtained by the continuous method with the electrode in the common carotid artery showed without exception a rise in acidity of the circulating blood on exposure to high oxygen pressure. The acidity curve of one of these experiments is shown in Fig. 5, record II. Measuring from the basal drift and expressing therefrom the E.M.F. in terms of *pH* indicates a change to the acid direction of approximately 0.13 *pH* during the exposure to oxygen at a pressure of 3200 mm. Hg. With decompression which was slow and continuous there occurred an alkaline change.

In the later experiments in which respiration was recorded, the animals obtained their oxygen supply from the spirometer, which, with the chamber, was carefully washed out with pure oxygen preceding compression. To ascertain whether there was any accumulation of carbon dioxide in the spirometer, samples of the spirometer gas were analysed in several experiments and no carbon dioxide was found.

In twenty-one of twenty-three experiments in which the electrode was placed in the arterial or venous blood, the results indicated an acid trend (the two exceptions showed a slight decrease in acidity) on exposure to high oxygen pressure. The increase in acidity in the different experiments varied in degree from 0.05 to 0.19 *pH*. The smaller acidity changes were accompanied by the greater hyperpnœas. The acidity curves retraced from the smoked records of two of these experiments are shown in records I and III of Fig. 5. Record I indicates an acid rise equivalent to a *pH* change of about 0.18. Both of these records were obtained from changes which occurred in the venous blood. A respiratory minute volume increase of 50 p.c. accompanied record I, while in the case of record III there was an increase of 40 p.c. Record III is of especial interest in that the first decompression to 2400 mm. Hg initiated only a slight decrease in blood acidity, while the second decompression to

1600 mm. produced a marked fall in acidity. The absence of any decided decrease in acidity until after the pressure had been lowered to below three atmospheres is an indication that the coordination of the dual function of the hæmoglobin was involved, since at three or more atmospheres the plasma holds sufficient oxygen in simple solution to supply the needs of the tissues. Reduction of hæmoglobin theoretically occurs only below three atmospheres pressure. Although decompression to one atmosphere of pure oxygen gave an initial decrease in the acidity as seen in both curves I and III of Fig. 5, a later secondary increase in

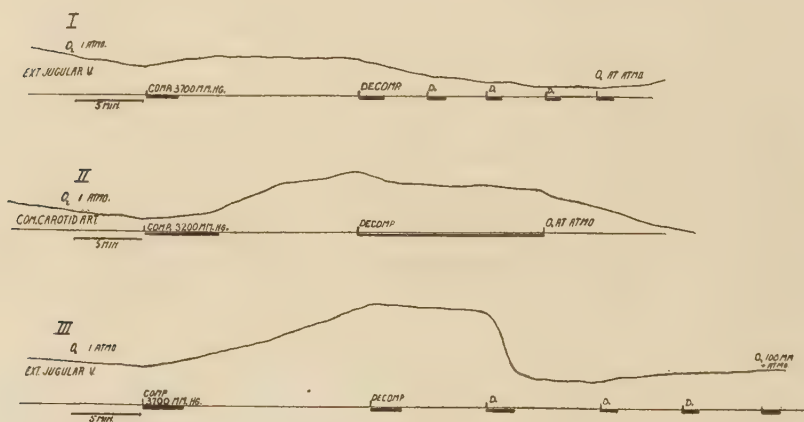


Fig. 5. Records of acidity changes as obtained by continuous method with animal exposed to high pressures of pure oxygen. Note the sharp decrease in acidity in III on second decompression at which point the pressure was just below three atmospheres. Note also the secondary increase in acidity after reaching atmospheric pressure in I, and 100 mm. + atmo. in III.

acidity developed. This secondary increase was also accompanied by an increase in the respiratory minute volume.

In another series of five experiments, records of changes in the acidity of both the arterial and venous blood were obtained simultaneously by the continuous method. Both bloods showed an increase in acidity on exposure to high oxygen pressure, but while there may have been a greater increase in acidity on the venous side of the circulation it was not demonstrated in any striking manner.

It seemed advisable to determine the acidity changes by other than the manganese-dioxide electrode method. To this end a series of eleven experiments was run in which samples were taken from the circulating arterial and venous bloods. Hæmolysis of the blood by rupture of the

blood cells on withdrawing the sample prevented the use of the quinhydrone electrode [Cullen and Biilmann, 1925]. This hæmolysis also offered some difficulty in the use of the Hastings' [1930] hydrogen ion colorimeter, but all of the experiments in which this method was used showed a definite acid change confirming the results obtained by the continuous method.

Heparinized fresh blood was subjected to high oxygen pressure and the acidity followed by the continuous method. In five such experiments no change was noted even after an exposure to 4.5 atmospheres of pure oxygen for an hour. The acidity changes noted in the animal experiments must then have been due to the involvement of the tissues and not to



Fig. 6. Portions of records showing progressive changes in ventilation and pulse rate brought about by exposure to and subsequent decompression from high oxygen pressure; I, animal breathing pure oxygen at 740 mm. Hg; II, seven minutes after raising pressure to 3650 mm.; III, after sixty minutes' exposure to 3650 mm. Hg; IV, first stage of decompression; decompression from IV to V was in four stages occupying seventy minutes; VI, thirty minutes after V.

a direct acid effect of high pressure of oxygen on the blood or the electrode. The absence of any marked change in acidity until after the pressure was lowered to less than three atmospheres as shown in record III, Fig. 5, is further evidence that the electrode was not affected by the high oxygen pressure.

Ventilation was followed in preliminary experiments by direct inspection of depth and rate of respiratory movements. The absence of any marked respiratory response may have been due to excessive anæsthesia. It is accepted that in deep anæsthesia CO₂ has little or no effect on total ventilation. In later experiments respiration was recorded by the spirometer. With few exceptions the respiratory minute volume was, as shown in Figs. 6 and 7, increased on exposure to high oxygen pressure. In some instances this increase was prompt, while in others

it was delayed. The increase was frequently associated with a decrease in respiratory rate, but in some experiments both rate and depth were increased. The delay in the increase of respiratory minute volume was in some cases preceded by an initial short decrease in rate and depth of respiration, but in others by no significant change. The early part of decompression brought about a decrease in the respiratory minute volume in many instances, but this decrease was frequently only temporary for, after lowering the pressure toward one atmosphere, there occurred in some cases a secondary increase in respiratory minute volume. Mention has already been made of the secondary rise in acidity which often accompanied the secondary increase in respiratory minute volume. The secondary increase in ventilation was also not infrequently temporary, and after a time returned toward pre-exposure values.

Oxygen absorption, which included oxygen consumption and that going into solution, was determined from the slope of the respiration record, due account being taken of the necessary temperature and pressure corrections. These determinations were made in forty-five experiments. Twenty-three of these indicated a decrease in oxygen absorption, beginning within about four minutes after the cessation of compression; thirteen, an initial increase followed later by a decided decrease to values below normal; eight, an increase with no later decrease; and another showed no change, due perhaps to too heavy anæsthesia. There occurred on decompression not only a return to the normal value of oxygen absorption but in most cases a marked overshooting as well. Graphic representations of the changes in oxygen absorption in some of the experiments are shown in Fig. 7.

So as not to confuse any decrease in oxygen consumption due to high oxygen pressure with a gradual harmful effect of heparin five experiments were carried out on non-heparinized animals. The results of these warranted the conclusion that heparin was not a determining factor in results obtained.

Volume flow of blood was followed in twenty-eight experiments. From experiments *in vitro* it had been found necessary to locate the thermopile outside the compression chamber and to insulate all the connecting tubes with cotton-wool to avoid thermal effects of compression and decompression. This arrangement also permitted the direct inspection of the blood colour as the blood flowed through the thermopile vessel (see Figs. 1 and 1 A). Three of these experiments showed only a very slight increase in volume flow of blood with increased oxygen pressure; in the others there was no significant change except in those in which periodicity

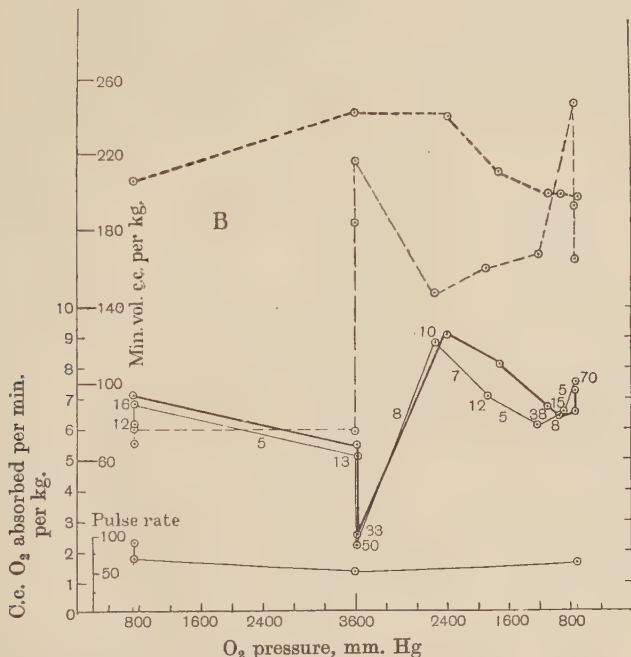
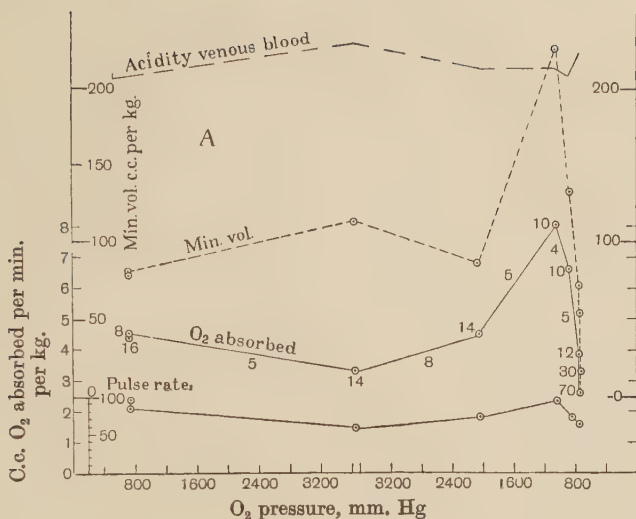


Fig. 7. Simultaneous changes in blood acidity, respiratory minute volume, oxygen consumption and pulse rate are plotted as ordinates against oxygen pressure on abscissæ. The numbers at each point on the oxygen consumption line represent duration in minutes of the exposure to that particular pressure. The time elapsing between exposure and during which alterations in pressure were made, is indicated along the line joining the various points. The acidity changes are plotted as inverted pH curves, absolute values are not given.

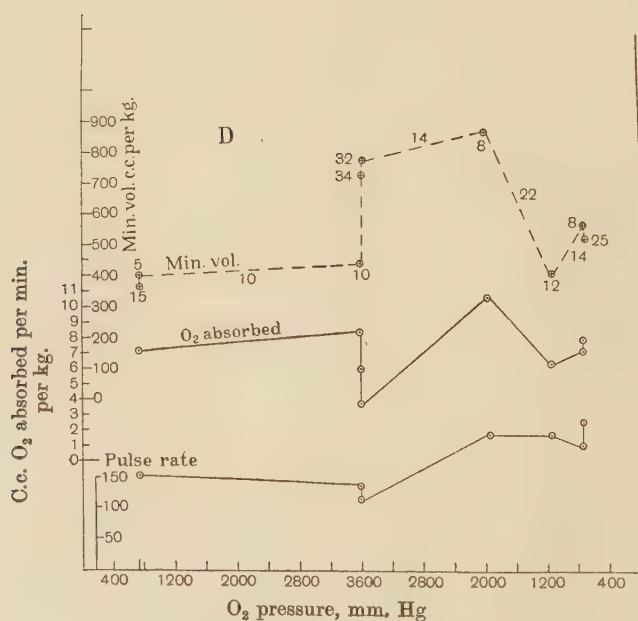
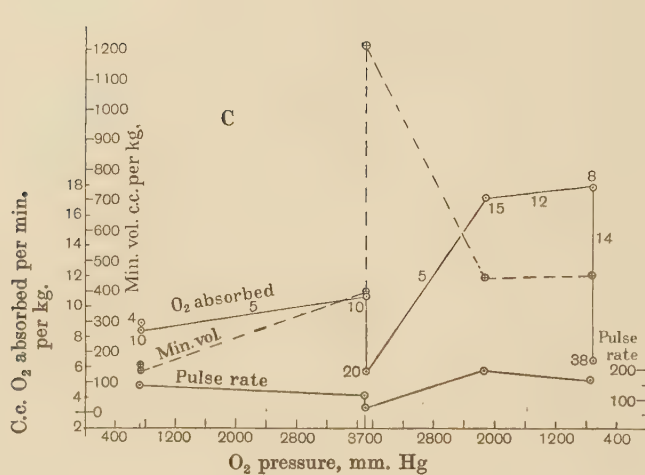


Fig. 7. Same as A and B.

in volume flow of blood, respiration, blood colour, blood-pressure, and heart rate, occurred.

Blood colour changes were observed in all of those experiments in which volume flow of blood was followed. These experiments were about equally divided between the venous and arterial blood flow. The colour of the arterial blood seemed to increase slightly in brightness on compression from one atmosphere of pure oxygen to four or five atmospheres, thus making the subsequent increase in respiratory minute volume the most significant. On decompression to one atmosphere there occurred a darkening, in some instances to a point darker than the pre-compression colour, and this even though the lungs were presumably still filled with pure oxygen. This darkening of the arterial blood was most marked in those cases which on return to atmospheric pressure showed an increase in respiratory minute volume. The changes in venous blood were even more striking. The very prompt change in the venous blood to a bright arterial colour during compression indicated the extent of physical solution of oxygen in the arterial blood. In several experiments in which the circulating vertebral venous blood was observed the colour changes conformed to those of the general circulation. In other experiments in which periodic respiration occurred there were accompanying periodic changes in the colour of the circulating blood. Simultaneous observations on the colour of the arterial and venous blood were made in those experiments in which acid changes in both venous and arterial blood were recorded. Prompt alterations in colour occurred in both bloods.

The frothing and hæmolysis found in all those samples of blood withdrawn from the animal under pressure indicated supersaturation of the blood with oxygen. From experiments *in vitro* it was found that no hæmolysis occurred as a result of decompression, from four atmospheres oxygen pressure, occupying a period of two minutes, but if this same blood was instantly released from pressure by withdrawing it through a small stopcock to the exterior of the tank, marked hæmolysis occurred. It would seem then that the hæmolysis of the blood drawn directly from the animal was due to mechanical rupture of red blood cells and not to some chemical action taking place within the animal.

The blood-pressure increased in only five of sixty-one experiments. The others showed no change or a slight decrease. In all but four experiments exposure to increased oxygen pressure was attended by a decrease in heart rate, and decompression by an increase, in many instances to values higher than the pre-compression record. The four exceptions showed an increase in heart rate on exposure.

In Fig. 7 A, B, C, D, are shown graphically the results of a few experiments, which serve to relate the changes occurring simultaneously in blood acidity, respiratory minute volume, oxygen absorption and pulse rate. No appreciable change occurred in respiratory minute volume or oxygen absorption in Graph A after breathing pure oxygen at one atmosphere for successive periods of eight and sixteen minutes, while blood acidity and pulse rate decreased. With raising the pressure up to 3650 mm. Hg and after a relatively short exposure (fourteen minutes), the acidity of the venous blood and respiratory minute volume increased, oxygen absorption and pulse rate decreased. During decompression to 2000 mm. Hg (occupying eight minutes) and subsequent exposure to this new pressure for fourteen minutes the changes noted during compression were reversed. The decrease in respiratory minute volume during early decompression was, however, only temporary. With a lowering of pressure to 1200 mm. Hg in five minutes and subsequent exposure to this pressure for ten minutes the oxygen absorption increased, overshooting the normal by 100 p.c. Respiratory minute volume increased 200 p.c., pulse rate rose slightly above normal and the fall in blood acidity was slowed. The next decompression stage gave a decrease in acidity, a marked fall in respiratory minute volume and pulse rate. With further decompression to one atmosphere of pure oxygen further decrease occurred in all the curves. After one hour and fifty-two minutes of breathing oxygen at one atmosphere, complete apnoea came on, acidity increased, and periodicity in respiratory minute volume, volume flow of blood, pulse rate, blood-pressure and blood colour ensued.

In the next experiment (Graph B) there were two successive exposures. The thin continuous line and the thin broken line represent oxygen consumption and respiratory minute volume respectively for the first exposure to increased oxygen pressure, while the heavy continuous line and the heavy broken line correspond to the second exposure. The initial and continued decrease in oxygen absorption during the first exposure to oxygen pressure of 3600 mm. Hg, the overshooting of oxygen absorption and its later fall toward normal during decompression and subsequent tendency to rise again at one atmosphere oxygen are about duplicated in the second exposure. The respiratory minute volume after thirteen minutes' exposure was altered very little from its value at one atmosphere pressure of oxygen, but after thirty-three minutes it had increased from 80 to 190 c.c. per min. per kg., and after fifty minutes more at a pressure of 3600 mm. it had risen to 210 c.c. The first stage of decompression tended to bring the respiratory minute volume to normal in the first

exposure curve, but further decompression increased respiratory minute volume to four times the normal obtaining at the beginning of the experiment. Seventy minutes later this hyperpnœa had decreased but not to normal. The increase in the respiratory minute volume during the second exposure was less than that of the first, and the decrease occurred later in decompression. The general level of respiratory minute volume during the second compression was much above that of the first. Pulse rate during the first exposure decreased, but not to such an extent as that shown during the exposure to one atmosphere preceding the compression. Clot formation prevented the obtaining of a record of pulse rate during the second exposure.

Graph C shows an initial increase in oxygen absorption followed by a later decrease on exposure to increased pressure. The temporary secondary respiratory minute volume increase is absent. Graph D shows a similar initial increase in oxygen absorption. The initial decrease in respiratory minute volume occurred relatively late in decompression.

DISCUSSION.

The volume flow of blood through the respiratory centre plays a very significant rôle in respiratory control [Gesell, Capp and Foote, 1922; Gesell, 1922]. Perhaps of equal importance is the character or composition of this circulating fluid, especially as relating to its efficiency as a carrier of those substances which directly or indirectly contribute to the removal of acid from the region. Christiansen, Douglas and Haldane [1914] showed that when hæmoglobin loses oxygen it becomes more basic, and under normal conditions the carbon dioxide liberated at the tissues is about neutralized by the base provided by the reduction of hæmoglobin [Werigo, 1892; L. J. Henderson, 1920]. The upsetting of this inter-relation at any point in the cycle constitutes a "broken coordination of the dual function of the hæmoglobin" [Gesell, 1923]. Among the conditions which might bring about such an upset, have been cited carbon monoxide poisoning, lowered alveolar oxygen, hæmorrhage, cardiac decompensation, anæmia, cyanide poisoning, and oxygen poisoning [Gesell, 1925], all of which are attended by alteration in respiratory activity.

Under normal conditions the blood contains about 19 volumes p.c. of oxygen. On subjecting it to three atmospheres pure oxygen about 6 c.c. additional are taken up in simple solution. Normally this is about the amount which is lost on passing through the tissue. Therefore, during exposure to three atmospheres of pure oxygen the tissues should receive

all their oxygen from the plasma, leaving the hæmoglobin completely oxidized. "It follows other things remaining constant that an animal subjected to three atmospheres of pure oxygen is totally robbed of the potential alkalinity of its hæmoglobin" [Gesell, 1923].

Even assuming that carbon dioxide is carried in significant amounts as carbhæmoglobin [Henriques, 1929]—recently questioned by Van Slyke and Hawkins [1930]—the carbon dioxide dissociation curves of oxidized and reduced hæmoglobin of Henriques still indicate the importance of the dual function of hæmoglobin.

The respiratory response in animals exposed to high tensions of oxygen, as observed by many investigators [Bert, 1878; Smith, 1899; L. Hill, 1908; Hill and Macleod, 1903; Gesell, 1923; and others], might well be taken as confirmatory evidence of disturbance in the acid transport. Gesell [1923] finds that intact rats subjected to high oxygen tension are very sensitive to administration of carbon dioxide. The results of the present investigation, of which a preliminary report has been given [Bean, 1929], point conclusively to an increased acidity of the blood with an accompanying accumulation of acid in the tissues of animals exposed to high pressures of pure oxygen. Such conclusions are supported not only by the information gained from experiments in which the manganese-dioxide electrode method was employed but also by the results of later experiments in which the colorimetric method was used on drawn samples of blood. The marked frothing of the venous blood drawn from the animals under pressure is strong evidence of the supersaturation of the blood with oxygen. This bubble formation which took place throughout the sample provided an especially efficient means of removing from solution the dissolved carbon dioxide of the blood. This removal would leave the sample with a lower acidity than that obtaining in the circulation. The acid results seen in those samples withdrawn while under pressure become then more significant, and help to establish the validity of the acid results obtained by the electrode method.

Record III, Fig. 5, is of especial interest since it shows that a marked decrease in acidity occurred only after the pressure was diminished to below three atmospheres, at which point the normal mechanism of acid transport should again begin to be effective. The secondary rise in acidity which occurred in some experiments following the alkaline change during decompression is not to be attributed to a supersaturation of the blood with oxygen but rather perhaps to an impairment of removal of carbon dioxide and a lack of proper oxygenation, thus involving the dual function of the hæmoglobin in quite a different way. This may have

been occasioned by a possible alteration in lung epithelium brought about by the exposure to oxygen [Smith, 1899]. The darkening of the blood after decompression in some experiments supports this view.

The general increase in the respiratory minute volume as seen on exposure of animals to high oxygen pressure lends further support to the theory of disturbed acid transport. The acidity curves (Fig. 5) did not continue a rapid rise indefinitely as the exposure was prolonged. Thus, with increased ventilation, a progressively slower rise in acidity occurred as exposure continued. In some instances of increased ventilation a relatively constant acid level was reached. The respiratory minute volume may be increased during exposure to high oxygen pressure by an increase in depth alone, since in some of the experiments showing increased minute volume the rate was slowed. This slowing of respiratory rhythm is a reaction which sometimes occurs on the administration of carbon dioxide, but apparently not with impaired oxidation from lowered alveolar oxygen.

The finding that oxygen absorption is diminished in animals exposed to high oxygen pressure calls for some analysis, especially since in a few experiments the diminution was preceded by an early increase. This early increase might conceivably be due to that oxygen which is being taken up in simple solution. Hill and Greenwood [1907 *b*] believed complete saturation of tissues with nitrogen to occur in about ten minutes after exposure to air at three atmospheres pressure, agreeing in principle with V. Schrötter [1904]. It is estimated [Haldane, 1927] that in the case of nitrogen less than twenty rounds of circulation are necessary for the body to reach half saturation under increased pressures of air, *i.e.* about ten minutes. For the dog, whose rate of circulation is faster than that of man, the half-saturation value should be reached in less time. It may, therefore, be that in those experiments in which initial increase in oxygen absorption was absent, the process of saturation had been about completed during the period in which the oxygen pressure was being raised. Hill and Macleod [1903 *b*], however, maintained that only after considerable time is the distribution corresponding to Dalton's Law obtained. If this be true the decrease in oxygen consumption as observed in the present investigation must be the more pronounced, since in spite of the amount going into solution the absorption values decrease.

Another explanation of the delay in the diminution of oxygen absorption is suggested in the relation of acidity to metabolic rate. Increased acidity of the tissues tends to lower oxidations. From the

acidity curves (Fig. 5) it is seen that while the acid change follows very soon after the compression it is gradual. We would expect then that if decreased oxygen consumption is a result of acidity, it would become progressively more marked throughout exposure—in other words the reduction of oxidations would be secondary to the development of acidity—which is borne out by experiment.

The overshooting of oxidations is indicative of accumulation of metabolites. It thus appears that oxidations are reduced during the high pressure in spite of the combination of increasing accumulation of oxidizable material and high oxygen pressure. They are increased with decompression despite a reduction in oxygen pressure. This again suggests the importance of acidity.

It is quite possible that in some of the present experiments there occurred irreversible changes or pneumonic conditions in the lungs, but it is not likely that such were the determining factors in the oxygen absorption results obtained in our acute experiments. The oxygen absorption line in Fig. 7 B of the second exposure approximates very closely to the corresponding line of the first exposure. Had there been a thickening of lung epithelium or a pneumonic condition which would have tended to cut down oxygen diffusion it would [Binger, Faulkner and Moore, 1927] seem as though the second oxygen line should have been lower than that of the primary exposure. From the graph it is seen to be actually higher. There must, however, have been some alteration in the conditions as a result of the first exposure, since the general level of the respiratory minute volume line is higher for the second exposure than for the first. It may be that the greater oxygen absorption in the second exposure was consequent upon the greater muscular effort accompanying the greater ventilation [Liljestrand, 1917]. If the lung changes had been effective in lowering the diffusion of oxygen the overshooting of oxygen absorption mentioned above would probably not have been present.

The belief that oxygen poisoning involves some important causal factor other than lung damage is supported by the experiments of Bornstein and Stroink [1912] who find that lung changes in animals exposed to five atmospheres of oxygen for from two to six hours are more marked than in those which die with a much shorter exposure to seven atmospheres of oxygen. They conclude that the cramps observed during exposure and the death of the animals are not due to lung oedema. The deleterious effect of high oxygen pressures on some bacteria [Novy and Soule, 1925] cannot, however, be explained either on the basis of

a broken coordination of the dual function of hæmoglobin or on lung damage. It may be that this action of oxygen on living cells is an additional contributing factor in the oxygen poisoning seen in mammals.

The diminished carbon dioxide output of animals exposed to high oxygen pressure found by Smith [1899] was interpreted by him as being due to an inflammatory condition of the lung consequent upon the exposure. Similar results obtained by Hill and Macleod [1903 *a*] are thought by them to be a result of a reduction in oxidations, since the decrease in carbon dioxide output occurs before the pneumonic condition is set up in the lungs. The lowering of body temperature as observed in the same experiments is believed by these authors to be further evidence of decreased oxidations. No lowering of the body temperature as determined by rectal thermometer was found in the experimental animals of the present study, neither was there any evidence from which it might be concluded that the cooling effect of compressed gas due to its increased thermal conductivity is a contributing factor in oxygen poisoning [Hill and Macleod, 1903 *c*]. No cases were found in which any moisture was felt on the animal's fur.

Dautrebande and Haldane [1921] attempted to determine whether the tissues of the nervous system are protected against the influence of oxygen by a diminution of circulation through them, thus lowering the oxygen pressure in the tissues. Any fall in alveolar carbon dioxide pressure when oxygen at increased pressure was breathed was to be taken as an indication of a decreased blood flow. Observing a decided fall in alveolar carbon dioxide tension—as had others [Bert, 1878; Hill and Macleod, 1903 *a*]—they conclude that the increased ventilation and diminished pulse rate obtaining during exposure to increased oxygen pressure is brought about by a slowing of the blood through the tissues. The colour and the frothing of the venous blood as observed in the present study, however, offer strong evidence of the supersaturation and non-reduction of oxyhæmoglobin as it passes through the tissues.

The direct measurement of blood volume flow shows that there is no decrease in circulation, and there are a few cases which suggest that there is even a slight increase. Granting that the broken coordination of the dual function does play an important rôle in oxygen poisoning, an increase in flow could be as logically expected as a protective mechanism against an accumulation of acid. Campbell [1930], in recent experiments, strongly supporting the belief in a disturbed acid transport in oxygen poisoning, implies an involvement of a vaso-constriction in the accumulation of carbon dioxide in the tissues under high oxygen pressure,

and has included it, perhaps unnecessarily, with the logical explanation based on the broken coordination of the dual function of the hæmoglobin as proposed by Gesell [1923]. The carotid blood flow quite likely parallels the vertebral flow [Bronk and Gesell, 1927; Bernthal, Bronk, Cordero and Gesell, 1927]. The absence of a decrease in carotid flow in experiments of the present study then indicates an absence of a vaso-constriction in the brain to protect it from the high pressures of oxygen. The change from a venous to a bright arterial colour in vertebral venous blood of animals on exposure to high oxygen pressure, and the frothing of the same blood in withdrawn samples, are more direct evidence that the blood flow is not slowed up through the brain to the extent that normal reduction occurs. Still further evidence that there is no decrease in blood flow during exposure to high oxygen pressure is found in experiments [Hill, 1908] in which there was no observable change in the wing of a bat or the web of a frog's foot when exposed to seventy atmospheres of air which is equivalent to fourteen atmospheres of pure oxygen.

SUMMARY.

Assuming that the blood holds 6 p.c. of oxygen in simple solution, when a resting animal is exposed to three atmospheres of oxygen the tissues should obtain their necessary oxygen without the reduction of hæmoglobin. This leading to a failure of liberation of base and a consequent broken coordination of the dual function of the hæmoglobin, should give rise to an accumulation of acid within the tissues.

This hypothesis was tested in experiments on sixty-eight dogs subjected to high pressures (three to five atmospheres) of pure oxygen. Venous and arterial blood changes, respiratory minute volume, respiratory rate, oxygen consumption, blood-pressure, pulse rate and blood volume flow were followed continuously by especially constructed apparatus. Blood colour, frothing of blood and acidity were observed in drawn samples of blood. Rectal temperature was followed.

Exposure to three or more atmospheres of pure oxygen increased the acidity of the arterial and venous blood. Decompression resulted in a return toward normal acidity. This increase in hydrogen ion concentration of the blood was attributed to an accumulation of carbon dioxide within the tissues due in the main to a broken coordination of the dual function of hæmoglobin both in the tissues and at the lungs.

Exposure to high pressures of oxygen elicited an augmented pulmonary ventilation which commonly increased with continued exposure. Decompression was associated with a decreased pulmonary ventilation.

The progressive increase in ventilation and decrease in oxygen consumption with continued exposure to increased pressure, and a progressive accumulation of acid, suggested that both the increased ventilation and decreased oxygen consumption were related to changes in the hydrogen ion concentration of the tissues. On the other hand additional impairment of oxidation by a direct action of increased oxygen pressure was not excluded.

It is concluded that the effect of high oxygen pressure on pulmonary ventilation may be related to an accumulation of acid metabolites and to an altered oxidative state consequent upon the broken coordination of the dual function of the hæmoglobin.

Overshooting of oxygen consumption to values above normal commonly occurred during the early stages of recovery during decompression.

Rectal temperature observations indicated that the changes in oxygen consumption were not due to changes in the temperature of the animal.

The absence of decreased carotid flow of blood fails to support the view that active vaso-constriction occurs as a protective mechanism against high oxygen pressure in the tissues. This is also indicated by the bright arterial hue of the returning venous blood and by the invariable frothing of the venous blood on release from high pressures.

The decrease in oxygen consumption and the increase in acidity of tissue make it difficult to determine the relative effect of each on pulmonary ventilation.

The finding that the rate of respiratory movements may diminish with an increase in respiratory minute volume suggests an acid action, since such results are not infrequently obtained with the administration of carbon dioxide. The augmentation of respiratory rate suggests effects of impaired oxidations.

Exposure to increased oxygen pressure gave a decrease in pulse rate which is a result characteristic of carbon dioxide administration.

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